Early report

(7) Psoriasis

Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial

U Chaudhari, P Romano, L D Mulcahy, L T Dooley, D G Baker, A B Gottlieb

Summary

Background Currently available treatments for moderate to severe psoriasis are either incompletely effective in some patients, or are associated with toxic effects. Since tumour necrosis factor α (TNF-α) is thought to have a role in the pathogenesis of psoriasis, we did a double-blind, randomised trial to assess the clinical benefit and safety of infliximab—a monoclonal antibody against TNF-α.

Methods 33 patients with moderate to severe plaque psoriasis were randomly assigned intravenous placebo (n=11), infliximab 5 mg/kg (n=11), or infliximab 10 mg/kg (n=11) at weeks 0, 2, and 6. Patients were assessed at week 10 for the primary endpoint (score on the physician's global assessment [PGA]). Analysis was by intention to treat.

Findings Of the 33 patients enrolled, three dropped out. Nine of 11 (82%) patients in the infliximab 5 mg/kg group were responders (good, excellent, or clear rating on PGA), compared with two of 11 (18%) in the placebo group (difference 64% [95% CI 20–89], p=0·0089), and ten of 11 (91%) patients in the infliximab 10 mg/kg group were responders (difference from placebo 73% [30–94], p=0·0019). The median time to response was 4 weeks for patients in both infliximab groups. There were no serious adverse events, and infliximab was well tolerated.

Interpretation In this controlled trial, patients receiving the anti-TNF-α agent infliximab as monotherapy experienced a high degree of clinical benefit and rapid time to response in the treatment of moderate to severe plaque psoriasis compared with patients who received placebo. These findings suggest that TNF-α has a pivotal role in the pathogenesis of psoriasis.

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Clinical Research Center, UMDNJ-Robert Wood Johnson Medical School, 51 French Street, New Brunswick, NJ 08901-0019, USA (U Chaudhari MD, P Romano RN, Prof A B Gottlieb MD); **and Centocor Inc, Malvern, PA, USA** (L D Mulcahy, L T Dooley DrPH, D G Baker MD)

Correspondence to: Prof Alice B Gottlieb
(e-mail: gottliab@umdnj.edu)

Introduction

Psoriasis is a psychologically and physically disabling disease that affects 1–3% of the US and European population;[1] about 25% of patients have moderate to severe disease. The costs and other financial implications of caring for patients with psoriasis can result in lower quality of life for patients with more severe psoriasis.[2] Treatments approved by the US Food and Drug Administration for this class of patients include ciclosporin, methotrexate, acitretin, ultraviolet B (UVB), and ultraviolet A with psoralen (PUVA). Ciclosporin is the most effective of these treatments, but exposure to this drug can result in toxic effects such as hypertension and irreversible renal insufficiency.[3] Methotrexate can take 4–8 weeks to produce significant improvement, and there is a risk of toxic effects on the liver and bone marrow. Acitretin alone is only partly effective and rarely clears the disease. Additionally, it causes substantial mucocutaneous toxic effects and is a teratogen, as is methotrexate. UVB and PUVA require an intensive treatment regimen (about three times per week for many months), thereby reducing patients' compliance. Additionally, PUVA has been associated with skin cancers, including malignant melanoma. Overall, the treatments available for moderately to severely active psoriasis are either incompletely effective in some patients or are associated with serious toxic effects.[4] There is therefore a need for highly efficacious treatments that are safe to use in a long-term regimen.

The two major pathological lesions seen in psoriasis are epidermal hyperproliferation with abnormal differentiation, and inflammatory infiltration in the epidermis and dermis. These processes are mainly driven by activated T cells or antigen-presenting cells, which release various chemokines and cytokines that signal the keratinocyte to hyperproliferate, and which ultimately leads to abnormal differentiation.[5–9] These signalling molecules include tumour necrosis factor α (TNF-α), interleukin 6, interleukin 8, granulocyte macrophage colony stimulating factor, and interferon gamma. The cytokine TNF-α in particular is believed to have a major role in this process: increased concentrations have been detected in psoriatic skin lesions.[10] TNF-α, via activation of nuclear factor κB (NFκB), induces synthesis of numerous cytokines, including interleukin 8, interleukin 6, and colony-stimulating factors. Also, TNF-α potentially contributes to the accumulation of inflammatory cells seen in epidermis and dermis by inducing expression of intracellular adhesion molecule (ICAM)-1 on endothelial cells and keratinocytes.[11] TNF-α therefore has a potential role in both of the major pathological lesions in psoriasis.[9] Consequently, blockade of TNF-α activity should, in theory, reduce inflammation and keratinocyte proliferation and differentiation abnormalities in psoriasis.

Infliximab is a chimeric monoclonal antibody that has high specificity, affinity, and avidity for TNF-α[12] and is currently approved in the USA and Europe for the treatment of rheumatoid arthritis and Crohn's disease.

The scientific rationale for blocking TNF-α in psoriasis and our own anecdotal experience with infliximab in psoriatic patients[13] led us to design a randomised, placebo-controlled trial of infliximab monotherapy in patients with moderate to severe psoriasis.

Patients and methods

Patients

Adult patients who had moderate to severe plaque psoriasis involving at least 5% of the body surface area and who were in good general health were referred to us by the Divisions of Dermatology and Clinical Pharmacology at UMDNJ-Robert Wood Johnson Medical School or were identified through general advertisements. Patients had a history of plaque psoriasis for a minimum of 6 months and a history of topical corticosteriod failure. All patients had a clear chest radiograph within 1 month of receiving the first dose of study medication. Patients who had used topical therapy in the previous 14 days or systemic therapy in the previous 28 days, or who had received treatment with anti-TNF-α monoclonal antibodies, human or murine immunoglobulins, TNF-α receptor fusion proteins, or other bioengineered fusion proteins were excluded from the study. Patients who had received previous immunobiologicals were also excluded. Patients were excluded from study participation for any of the following reasons: positivity for HIV, hepatitis B surface antigen, or hepatitis C; history of current alcohol or drug abuse; history indicating serious infections such as hepatitis, pneumonia, or pyelonephritis in the previous 3 months; known history of active tuberculosis within the previous 5 years; history of malignancy within the previous 5 years or suspicious lymphadenophathy or splenomegaly on physical examination; or clinically significant laboratory abnormality. All patients provided written informed consent before inclusion in the study, and the study protocol was approved by the Institutional Review Board of the UMDNJ-Robert Wood Johnson Medical School.

Methods

Patients were randomly assigned placebo or infliximab 5 or 10 mg/kg at weeks 0, 2, and 6 in a 1/1/1 fashion by means of a block-of-six randomisation scheme. For every six patients enrolled, two were assigned infliximab 5 mg/kg, two were assigned infliximab 10 mg/kg, and two were assigned placebo. Intravenous placebo or infliximab was prepared by a research pharmacist who was aware of treatment assignment.

Infliximab (Remicade, Centocor, Malvern, PA, USA) was supplied in 20 mL vials containing 100 mg of the lyophilised concentrate. Placebo was supplied in an identical manner except that it did not contain infliximab. A vial was reconstituted with 10 mL of sterile water for injection (United States Pharmacopeia). The total dose was further diluted to 250 mL with 0.9% sodium chloride for injection (USP). The concentration of infliximab ranged from 1·2 to 6·8 g/L on the basis of the volume of infliximab given and the bodyweight of the patient. Infliximab infusion was always started within 3 h of preparation. The infliximab infusion solution was given by investigators unaware of treatment assignment with an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size of 1·2 μm). The solution was then given to the patient through a peripheral venous access site over 2 h. All investigators and patients were masked during the first 10 weeks of the study; only the pharmacist preparing the study medication knew the treatment assignment.

Patients did not use any other treatment for their psoriasis during the entire duration of the study, except for non-medicated emollients and non-prescription tar or salicylic shampoos. Patients stopped taking systemic therapy (UVB, PUVA, ciclosporin, methotrexate, or acitretin) at least 4 weeks before, and stopped using topical therapy at least 2 weeks before receiving the first dose of study medication.

Clinical and laboratory assessments were done at screening, baseline, and every 2 weeks thereafter until 10 weeks after the start of therapy. Clinical assessments included physical examinations, vital signs, concomitant medications, monitoring for adverse events, and measures of psoriasis activity (Psoriasis Area Severity Index [PASI],[14] Physician's Global Assessment [PGA], and photographs). For the PASI, patients are rated on the basis of erythema, scaling, and thickness divided in four anatomical parts (head, trunk, upper extremities, and lower extremities). The area of each anatomical part is factored into the overall value. The maximum PASI score is 72. The PGA is an overall assessment of a patient's psoriasis, taking into consideration the quality and extent of plaques relative to the baseline assessment.

Patients were monitored for the occurrence of all adverse events. All assessments were done in a masked manner. Laboratory assessments were made at various time points during the 10-week study period and included complete blood count, chemistries, anti-nuclear antibody concentration, urinalysis, and serum and urine β-human chorionic gonadotropin concentration. Clinically significant laboratory abnormalities that could not be attributed to other medical conditions were reported as adverse events.

The PGA at week 10 was the predefined primary efficacy endpoint. A positive response was defined as attaining a good (50–74% clearing with moderate improvement), excellent (75–99% clearing with striking improvement), or clear (100% clearing) rating on the PGA. Non-response was defined as a fair (25–49% clearing with slight improvement), poor (0–24% clearing with little or no change), or worse rating on the PGA. A supportive secondary endpoint was the PASI, where a favorable response was an improvement of at least 75% from the baseline PASI.

At week 10, all patients were categorised as either non-responders or responders and then the treatment assignment was revealed. Non-responders in the placebo group were subsequently randomised to receive open-label infliximab 5 or 10 mg/kg at weeks 10, 12, and 16. Responders in the placebo group were followed up for relapse and then offered infliximab in the same manner as the non-responders in the placebo group. Non-responders in the infliximab 5 mg/kg group were offered a single infusion of infliximab 10 mg/kg and followed up for response, whereas non-responders in the infliximab 10 mg/kg group were dropped from the study. Patients who responded to treatment with infliximab 5 or 10 mg/kg were followed up for relapse and offered single dose infusions of the drug upon relapse. The results of the initial 10-week double-blind study period are reported here.

Statistical analysis

With a planned sample size of ten patients per treatment group, the study had 85% power to detect a difference between the assumed placebo response rate of 10% compared with the assumed infliximab response rate of 70% with $\alpha=0{\cdot}05$. A Fisher's exact test was used to test the difference between the proportion of patients with a favorable response in each infliximab treatment group compared with the placebo group. A two-sided $\alpha=0{\cdot}05$

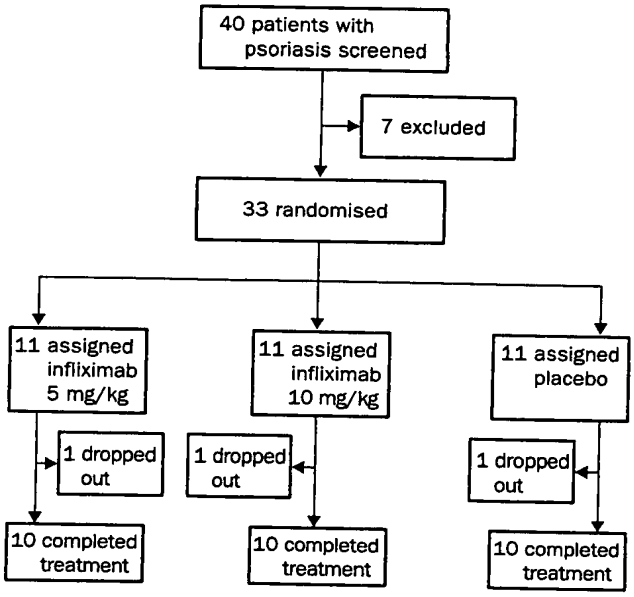

Figure 1: **Trial profile**

was regarded as significant. No adjustments for multiple testing were made. The primary analysis was done according to intention to treat—ie, all randomised patients were included in the analysis.

Results

Patients

33 patients, ranging in age from 21 to 69 years, were included in the study. 11 were assigned infliximab 5 mg/kg, 11 infliximab 10 mg/kg, and 11 placebo. Three patients withdrew during the course of the study, one from each treatment group (figure 1). One patient from the infliximab 5 mg/kg group was withdrawn at week 2, secondary to a mild rash. Another patient in the 10 mg/kg group was withdrawn, 7 days after his first infusion, because of worsening psoriasis. The third patient, in the placebo group, withdrew consent at week 6 due to a lack of improvement in his disease. The three patients withdrawn were counted as non-responders in their respective groups. A summary of baseline characteristics is provided in table 1. The three treatment groups were similar with regard to sex, age range, and baseline disease severity.

Efficacy

Nine of 11 (82%) patients in the infliximab 5 mg/kg group and ten of 11 (91%) in the infliximab 10 mg/kg group

	Placebo (n=11)	Infliximab 5 mg/kg (n=11)	Infliximab 10 mg/kg (n=11)
Sex (M/F)	8/3	7/4	8/3
Age (years)			
Mean (SD)	45 (12)	51 (14)	35 (11)
Range	29–68	27–69	21–50
Weight (kg)			
Mean (SD)	85 (19)	87 (20)	96 (27)
Range	62–100	62–118	61–165
PASI			
Mean (SD)	20·3 (5·5)	22·1 (11·5)	26·6 (10·3)
Range	13·8–31·9	10·0–42·6	14·8–42·0

PASI=psoriasis area severity index.

Table 1: **Baseline characteristics of study population**

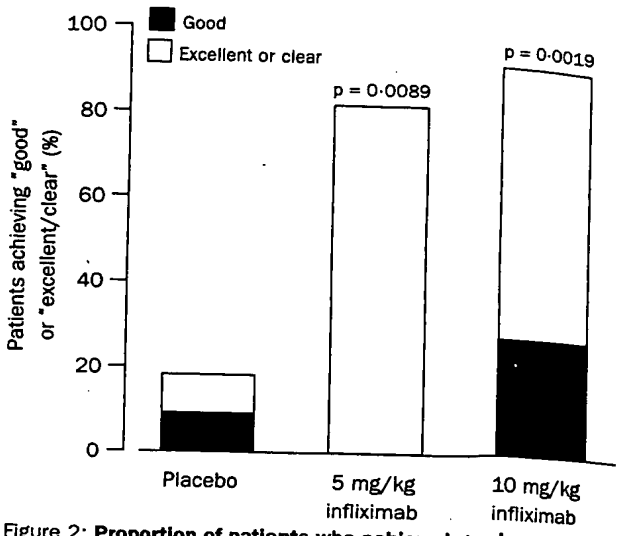

Figure 2: **Proportion of patients who achieved good or excellent/clear rating on physician's global assessment scale at week 10**

achieved the primary endpoint of a good, excellent, or clear rating on the PGA at week 10, compared with only two of 11 (18%) patients in the placebo group (difference between infliximab 5 mg/kg and placebo 64% [95% CI 20–89], p=0·0089; difference between infliximab 10 mg/kg and placebo 73% [30–94], p=0·0019; figure 2). All nine responders in the infliximab 5 mg/kg group had either an excellent or clear rating on the PGA, whereas seven of the ten responders in the infliximab 10 mg/kg group had either an excellent or clear rating on the PGA, and the other three had a good rating (figure 2).

The change in PASI score was a secondary endpoint. Nine of 11 (82%) in the infliximab 5 mg/kg group and eight of 11 (73%) patients in the infliximab 10 mg/kg group had at least 75% improvement in the PASI score, compared with two of 11 (18%) patients in the placebo group (difference between infliximab 5 mg/kg and placebo 64% [20–90], p=0·0089; and difference between infliximab 10 mg/kg and placebo 55% [9–85], p=0·03; figure 3). The mean PASI scores at baseline for the placebo and infliximab 5 and 10 mg/kg groups were 20·3, 22·1, and 26·6, respectively. At week 10, the respective

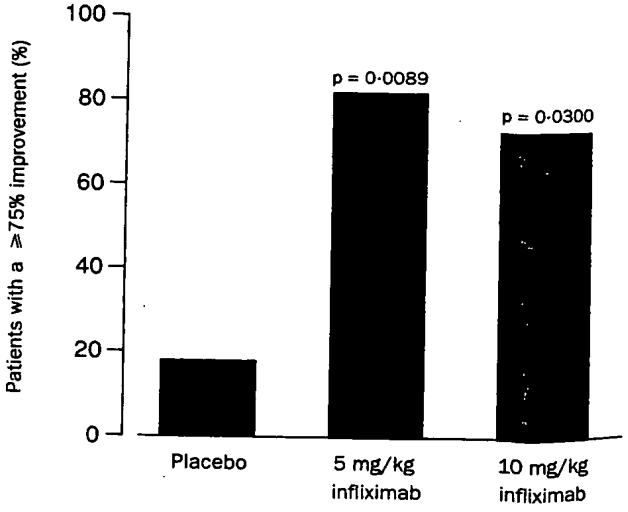

Figure 3: **Proportion of patients with 75% or more improvement in psoriasis area severity index**

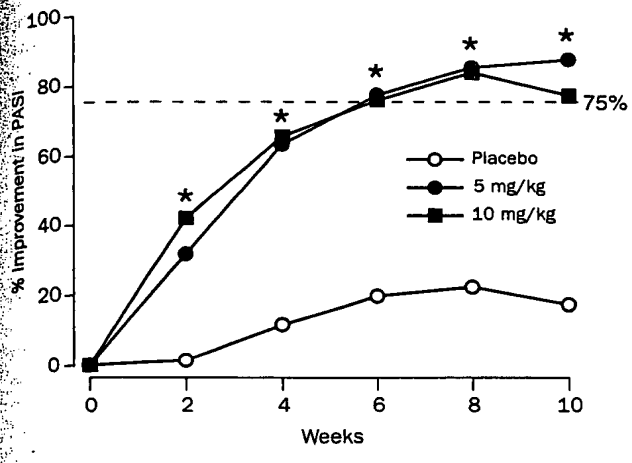

Figure 4: **Mean percentage improvement in psoriasis area severity index (PASI)**
*p<0·0003 for difference from placebo.

mean PASI scores were 17·5, 3·8, and 5·9. The mean percentage improvements in PASI scores were significantly (p<0·0003) higher among infliximab-treated patients as early as week 2 of therapy (figure 4). In both of the infliximab treatment groups, the median time to response was 4 weeks. Photographs illustrating the typical degree of improvement observed from baseline to week 10 with placebo, infliximab 5 mg/kg, and infliximab 10 mg/kg are shown in figure 5.

Adverse events

There were no serious adverse events. A summary of adverse events judged by the investigator to have a possible, probable, or definite relation to the study drug that occurred in two or more patients is shown in table 2. Headache was the only adverse event that occurred in a higher proportion of infliximab-treated patients than placebo controls. More reports of headache were made in the 10 mg/kg group than in the 5 mg/kg group. No infusion reactions were reported during the initial 10-week double-blind period. Of note, two patients who received infliximab 5 mg/kg had positive antinuclear antibody titres (1:160 and 1:320) at the final assessment

Adverse events	Placebo (n=11)	Infliximab 5 mg/kg (n=11)	Infliximab 10 mg/kg (n=11)
Headache	2	1	7
Upper respiratory infection	4	2	3
Abdominal bloating/ pain (non-specific)	1	2	1
Infection*	2	1	1
Increased AST†	1	0	2
Sore throat	0	1	2
Dysesthesia‡	1	1	0
Fever	0	0	2
Myalgia	0	1	1
Positive ANA titre (homogenous pattern)†	0	2	0
Pruritus	2	0	0
Rhinitis	1	1	0

AST=aspartate aminotransferase. ANA=antinuclear antibody. *Includes cellulitis and otitis externa in the placebo group, dental abscess in the infliximab 5 mg/kg group, and community-acquired pneumonia in the infliximab 10 mg/kg group. All infections responded to oral antibiotics. †Laboratory abnormalities were clinically significant and could not be explained by other medical conditions. ‡Includes pins/needles sensation in hand (placebo) and numbness/tingling (infliximab 5 mg/kg).

Table 2: **Adverse events reported by two or more patients**

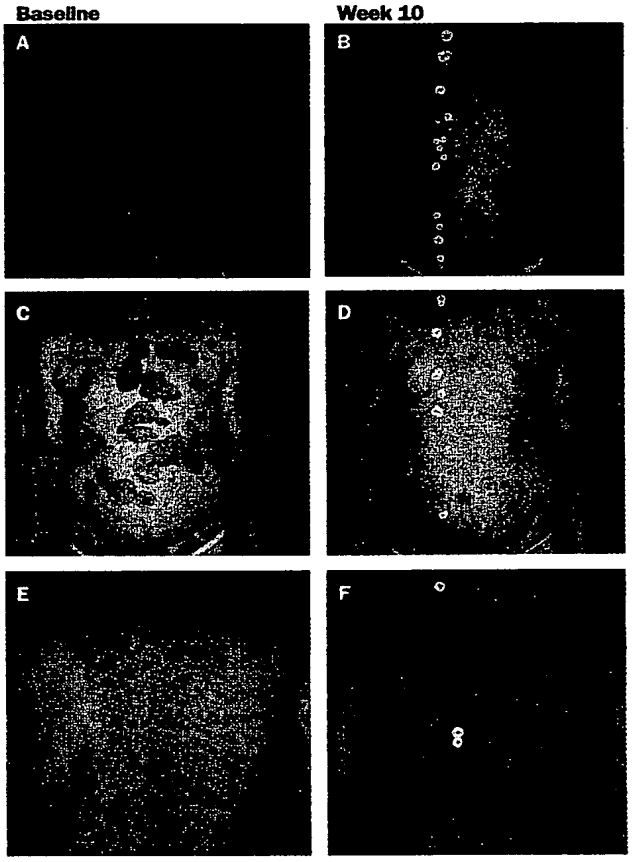

Figure 5: **Degree of improvement in psoriasis from baseline to week 10**
A and B=infliximab 5 mg/kg, C and D=infliximab 10 mg/kg, E and F=placebo.

(week 10) that were not present at baseline. Both of these patients, one who tested positive and one who had equivocal results for antibodies to double-stranded DNA, had no relevant clinical symptoms and responded well to infliximab therapy.

Discussion

This study was designed to assess the clinical benefit and safety of infliximab monotherapy in patients with moderate to severe plaque psoriasis. A second aim was to use infliximab as a targeted therapeutic probe to determine the role of TNF-α in the pathogenesis of psoriasis.

Patients who received infliximab in this study experienced a higher degree of clinical benefit and a more rapid time to response than patients who received placebo. The response seen was similar to that of ciclosporin in terms of response rate, extent, and rapidity of clearance.[3] Most responders (82%) had either an excellent or clear rating on the PGA and had at least 75% improvement from baseline based on the PASI score. There did not seem to be any clinically important difference between the infliximab 5 and 10 mg/kg doses with regard to efficacy. Infliximab was well tolerated by all study participants.

In the mid-1980s, the immunopathogenesis of psoriasis was elucidated. Specifically, activated T lymphocytes and expression of interferon gamma and TNF-α-induced proteins in keratinocytes were found in psoriatic plaques but not in uninvolved skin.[9] Insights into the underlying

pathogenesis of psoriasis have provided opportunities to target many of the key steps in the disease process, including T cell activation, cytokine expression, and lymphocyte trafficking. Biological agents assessed in the treatment of psoriasis owing to their role in blocking T-cell activation include a humanised monoclonal antibody against CD11a (hu1124), a primatised monoclonal antibody that binds specifically and with high affinity to CD80, alefacept (LFA3TIP), dacluzimab (a humanised antibody to the α subunit of the interleukin 2 receptor), and soluble CTLA4Ig.[15–19] In clinical assessments of these potential therapies that involved the PASI score, mean decreases from baseline ranged from 10% to 53%.[15,17,18] In the case of alefacept, 3 months of treatment was required to show a clinically meaningful response.[17] Therapies assessed on the basis of their ability to alter cytokine expression include interleukins 10 and 11, which can shift cytokine production from the Th1 to Th2 pattern.[20,21] Although modest efficacy was shown in initial assessments, further studies have not been reported to date. A monoclonal antibody to interleukin 8 (ABX-IL-8) has also been assessed in the treatment of moderate to severe psoriasis (Gerald G Krueger, personal communication). 45% of patients who received the most effective dose assessed (3 mg/kg) had improvements of 50% or better in the PASI score.

Etanercept is a soluble receptor fusion protein that inhibits TNF and has been assessed alone and in combination with methotrexate in patients with psoriatic arthritis.[22] In this assessment, 26% of patients treated with etanercept achieved at least 75% improvement in the PASI score, compared with none of the placebo-treated patients. The apparent lesser response of etanercept compared with infliximab might be explained by several factors, including differences in the population of patients studied, route of administration (subcutaneous for etanercept *vs* intravenous for infliximab), and ability to achieve cell lysis. Infliximab is capable of triggering complement-mediated lysis of TNF-α-expressing cells in vitro,[23] whereas etanercept does not seem to cause cell lysis.[24] Additionally, the infliximab/TNF-α complex is much more stable than the etanercept/TNF-α complex.[25] Therefore, for the biologicals tested to date, only 10–50% of patients achieved at least 75% improvement in the PASI score, compared with 70–80% of infliximab-treated patients in the current trial.

The data in this report show a response to infliximab similar to that seen with ciclosporin in terms of the high proportion of patients achieving clearance and the rapidity of clearance. Infliximab was well tolerated by the patients assessed in this trial. Ciclosporin therapy, however, can cause systemic hypertension, hepatotoxicity, and nephrotoxicity, and the risk of these side-effects increases with increasing dose and duration of therapy. Elderly patients are at particular risk of these side-effects. Also, most patients will experience rapid relapse of psoriasis upon cessation of ciclosporin treatment.[3] Although patients showed high clinical response rates to infliximab at 10 weeks in this study (4 weeks after the last infusion at week 6), the longer-term durability of the benefit needs to be established.

Findings from the present study provide proof that TNF-α is pivotal in the pathogenesis of psoriasis. TNF-α functions in several steps of this inflammatory process: it induces the expression of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1), both of which are involved in trafficking lymphocytes to inflammatory lesions.[26] Langerhans cells are one of the main antigen-presenting cells of the skin, which are responsible for activation of T cells. TNF-α is known to stimulate the migration of Langerhans cells to lymph nodes and enhance the capability to present antigen to primed T cells.[27] NFκB is a transcription factor that regulates the expression of genes that encode adhesion molecules, cytokines (that contribute to inflammation), and immune receptors. TNF-α is involved in the activation of NFκB, thereby contributing to the inflammation of psoriasis.[11] Infliximab can inactivate TNF-α that is soluble,[28] expressed on the cell surface, or even when it is associated with the TNF receptor. Therefore, infliximab could possibly have the ability to turn off already activated T cells in visible psoriatic plaques.

Infliximab has been studied extensively in the treatment of rheumatoid arthritis and Crohn's disease. Features of TNF activity such as cellular trafficking, cellular infiltration, and cellular proliferation have been assessed before and after infliximab therapy. Results of these assessments show that expression of adhesion molecules such as e-selectin and VCAM is greatly downregulated in the synovium or bowel mucosa in individuals with rheumatoid arthritis or Crohn's disease after infliximab therapy.[28,29] Similarly, cell trafficking as assessed by technetium-labelled white-blood-cell scintigraphy is substantially reduced within 4 weeks of infliximab administration in both rheumatoid arthritis and Crohn's disease.[30,31] Also, cellular infiltrates in synovial and bowel mucosa are greatly reduced by infliximab therapy,[29,32] and intracellular gene expression as controlled by NFκB is downregulated within 2 weeks of infliximab treatment in Crohn's disease.[33] Finally, CD3-positive lymphocyte proliferation is downregulated in the mucosa of patients with Crohn's disease who have received infliximab.[34] Therefore, substantial evidence supports the comprehensive nature of the effects of TNF-α blockade achieved by infliximab in rheumatoid arthritis and Crohn's disease. The precise pathways blocked by infliximab in individuals with psoriasis remain to be established. However, presumably, some combination of inflammatory downregulation mechanisms seen in infliximab-treated patients with rheumatoid arthritis or Crohn's disease also contributes to the benefit seen in the treatment of psoriasis with infliximab.

Further studies are required in this target population to firmly establish the safety and efficacy of infliximab in the treatment of moderate to severe psoriasis, especially for long-term treatment of this chronic disease. However, the clinical response to anti-TNF-α monotherapy in this trial suggests that, among the many cytokines and growth factors overexpressed in psoriatic plaques, TNF-α has a pivotal role in the pathogenesis of psoriasis.

Contributors

Alice B Gottlieb developed the hypotheses tested, designed the protocol, obtained funding, and submitted the study to the US Food and Drug Administration (FDA). She also participated in the execution of the study. Umesh Chaudhari and Pat Romano participated in the study execution and helped write and review the original protocol and consent form, amendments, and FDA submissions. Dan Baker and Lisa Mulcahy reviewed the protocol and helped monitor the study. Lisa Dooley was responsible for statistical design and analysis.

Acknowledgments

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